Sequencing of Systemic Therapies and Clinical Trial Options for Patients with Metastatic Squamous Cell Carcinoma

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Case Presentation

- 49 yo male presented with “pneumonia” Sept 2016
- Smoked 3 PPD for 30 years but quit 2015
- History – HTN, COPD, asthma
- Treated with two courses of antibiotics
- Chest x-ray – LLL mass with widened mediastinum
- Chest CT – 4.3-cm LLL mass, hilar and mediastinal adenopathy, multiple bone mets

Case Presentation

- Bronchoscopy/EBUS
- Pathology – squamous carcinoma in endobronchial biopsy as well as station 7 FNA
- PD-L1 – 25% mild to moderate membranous staining (SP263)
- PET/CT – confirmed CT findings as well as showing multiple bone mets particularly in lumbar spine
- Brain MRI – negative

Case Presentation

- Most of work-up done in New York
- Moved to Central Florida to be closer to family
- No insurance
- Initial clinical course characterized by increasing pain in lower back requiring admission for pain control – PS trending toward a solid ECOG PS 2
- MRI – extensive metastatic involvement of L4 has resulted in posterior displacement of the vertebral body margin, and very tight central canal stenosis
- Radiation oncology – recommended palliative course but initiation complicated by insurance issue

Case Presentation

- Discharged from hospital but required increasing doses of narcotics to control pain as outpatient
- Insurance issues persisted
- Recommended carboplatin/*nab* paclitaxel
- Seen in clinic on day 8 – “dramatic” improvement in pain

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Disclosures

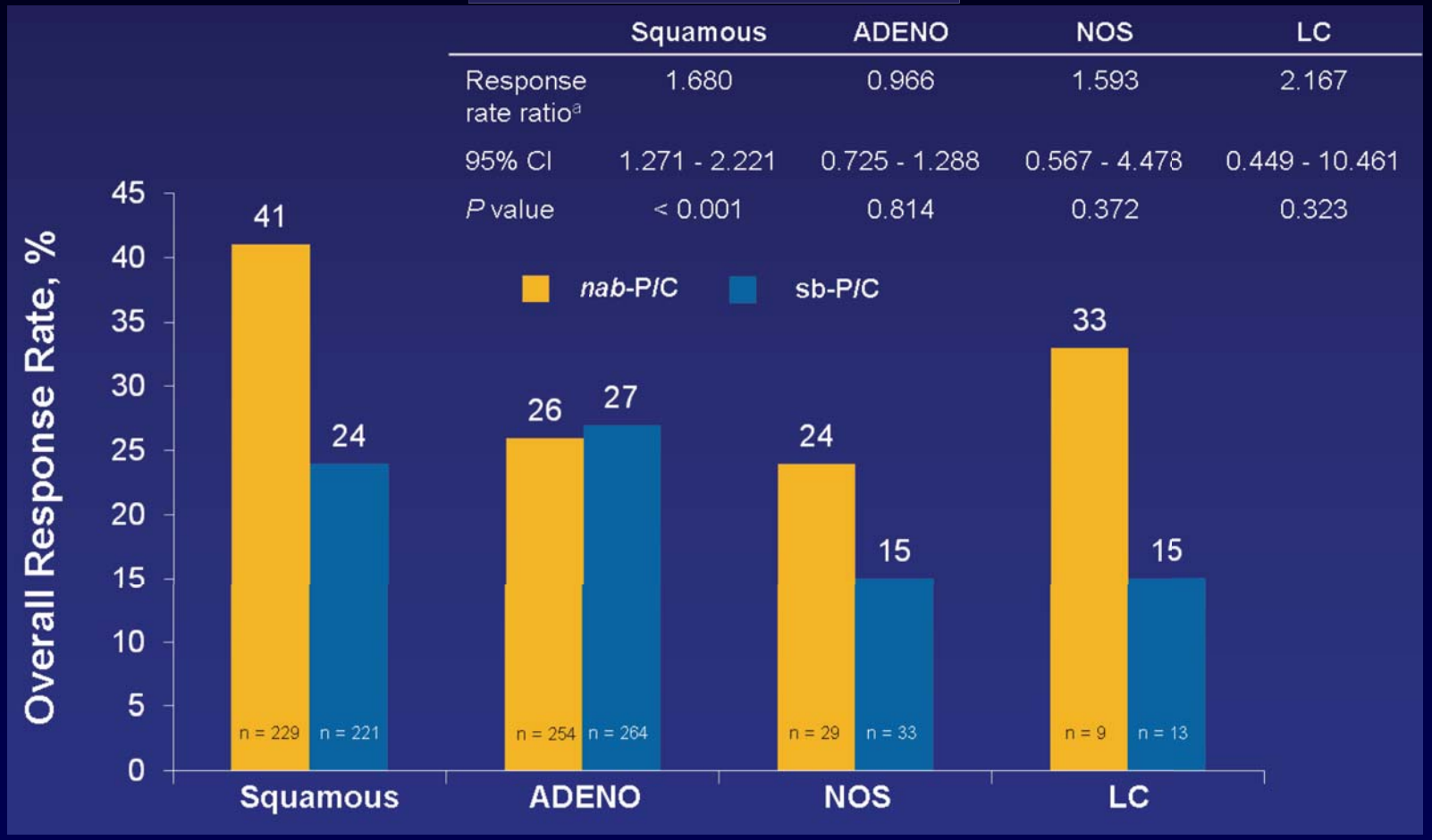
Advisory Committee	Bristol-Myers Squibb Company, Takeda Oncology
Contracted Research	AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Celgene Corporation, Genentech BioOncology, GlaxoSmithKline, Lilly, Pfizer Inc
Speakers Bureau	Bristol-Myers Squibb Company, Celgene Corporation, Genentech BioOncology

Key Take Home Points – Stage IV Squamous

- Active tobacco smoking has a greater association with squamous carcinoma than other subtypes of NSCLC
- Patients with squamous carcinoma typically have more co-morbidities compared to other subsets of lung cancer (often smoking-related)
- Actionable genotypes are rarely found in patients with squamous carcinoma (routine testing not recommended)
- Survival gains seen in non-squamous NSCLC have not been seen in squamous carcinoma patients
- Fewer therapeutic options exist for squamous carcinoma patients, who represent about 25% of all cases of NSCLC

Nab-Paclitaxel/Cb Vs sbPac/Cb -IRR of Overall Response Rate by Histology

	Squamous	ADENO	NOS	LC
Response rate ratio[a]	1.680	0.966	1.593	2.167
95% CI	1.271 - 2.221	0.725 - 1.288	0.567 - 4.478	0.449 - 10.461
P value	< 0.001	0.814	0.372	0.323

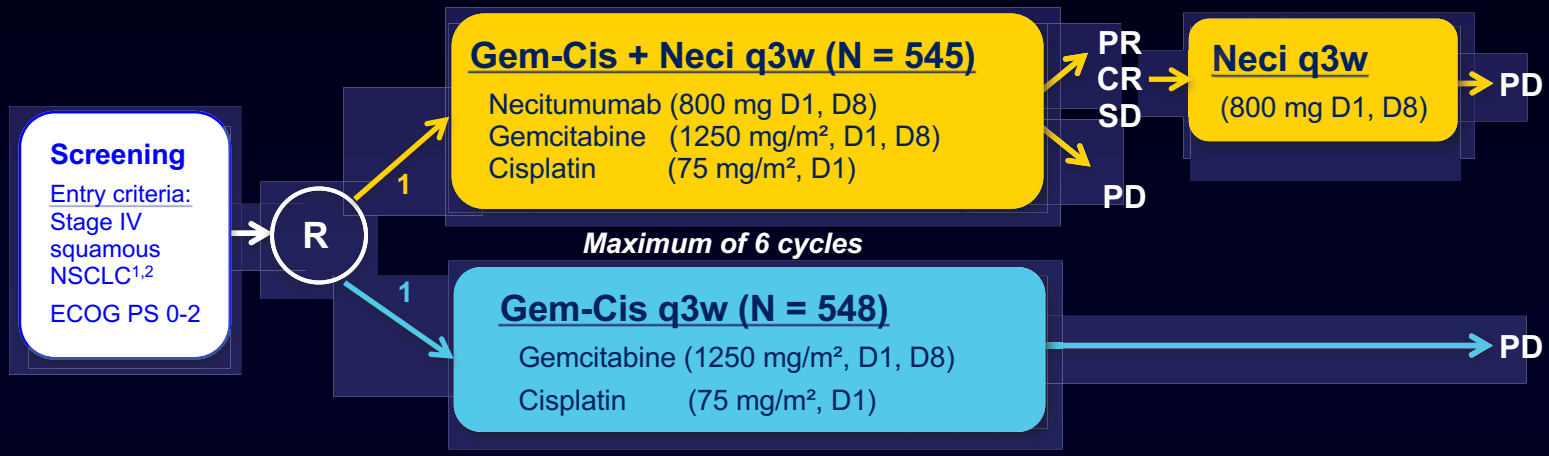


[a] 95% CIs for response rate ratios are calculated according to the asymptotic 95% CI of the relative risk of *nab*-PC to sb-PC.

ADENO, adenocarcinoma; CI, confidence interval; LC, large cell carcinoma; NOS, not otherwise specified; P/C, paclitaxel + carboplatin; sb, solvent-based; SCC, squamous cell carcinoma.

Socinski MA et al. *Ann Oncol* 24:2390-6, 2013.
Socinski MA et al. *J Clin Oncol* 30:2055-62, 2012.

SQUIRE: Necitumumab + CG Vs CG alone in Stage IV Squamous Carcinoma of the Lung



Randomization (R) stratified by: ECOG PS (0-1 vs. 2) and geographic region (North America, Europe and Australia; vs. South America, South Africa and India; vs. Eastern Asia)

Primary endpoint: Overall survival

Patient selection not based on EGFR protein expression

Radiographic tumor assessment (investigator read): at baseline and every 6 weeks until PD

Mandatory tissue collection

[1] AJCC TNM Classification, 7th edition, 2009; [2] UICC TNM Classification of Malignant Tumors, 7th edition, 2009

Thatcher N et al. *Lancet Oncology* 2015.

Primary Outcome: Overall Survival (ITT)

HR (95%CI): 0.84 (0.74, 0.96); p=0.012

ORR – 31.2% vs 28.8%, p=0.4

DCR – 81.8%vs 77.0%, p=0.04

PFS – HR = 0.85, p=0.02

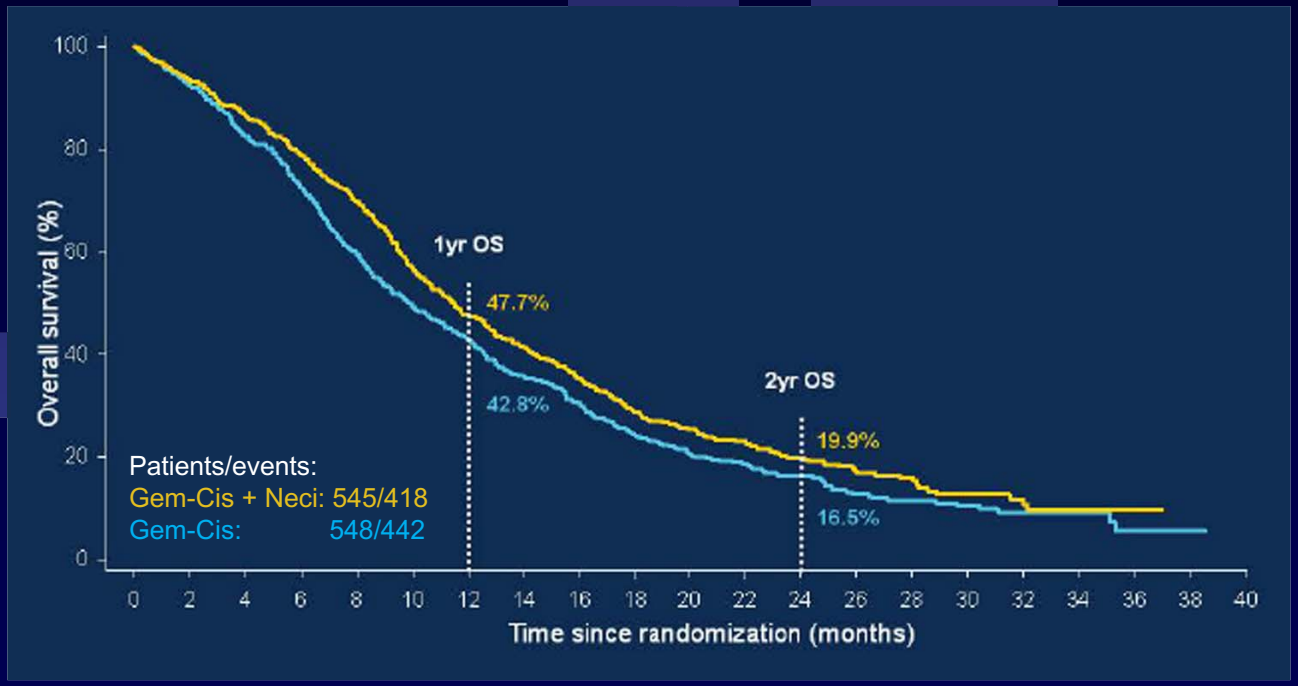
Exploratory H-score analysis using 200 as the cut-point – NS

Toxicities (≥ Gr 3) – Skin rash 7.0% vs <1%, hypomag 9.0% vs <1%, HSR 0.4% vs 0.0

Median OS (95%CI), months:

Gem-Cis + Neci: 11.5 (10.4, 12.6)

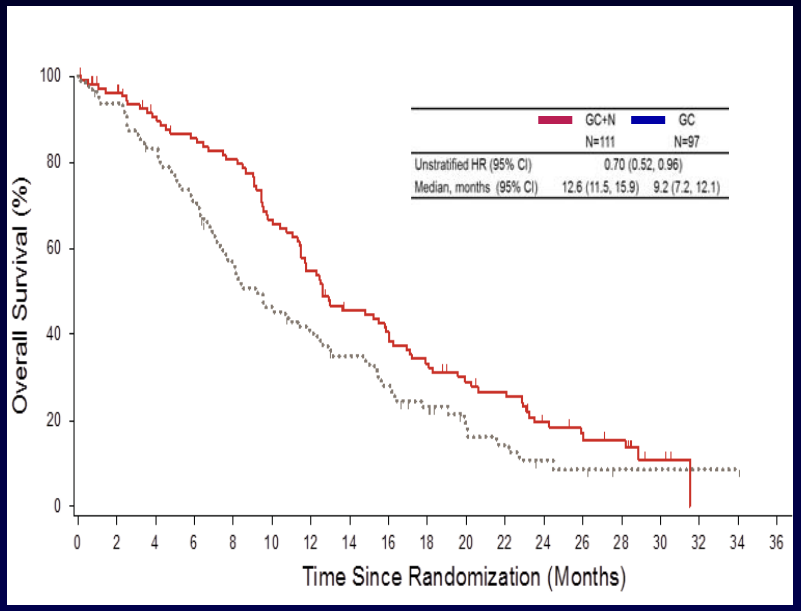
Gem-Cis: 9.9 (8.9, 11.1)



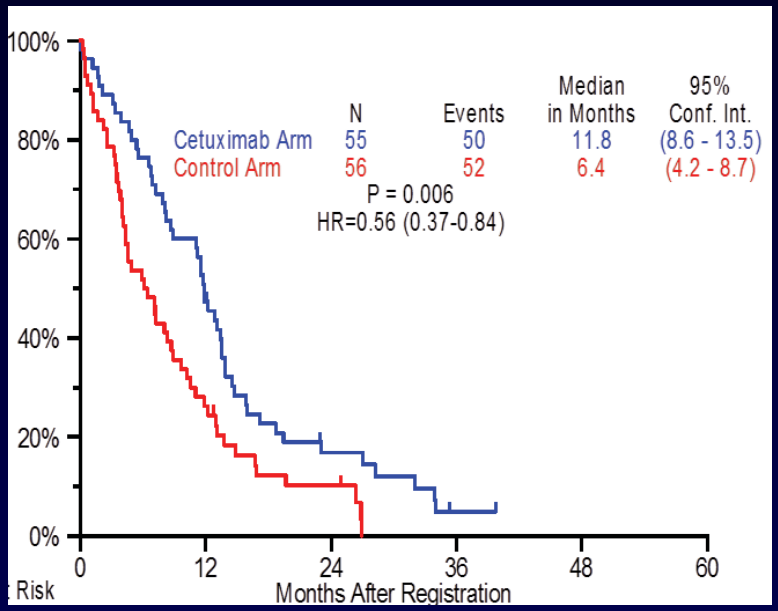
Thatcher N et al. *Lancet Oncology* 2015.

Overall Survival in Patients With EGFR-Positive NSCLC

SQUIRE (EGFR FISH+)[1]



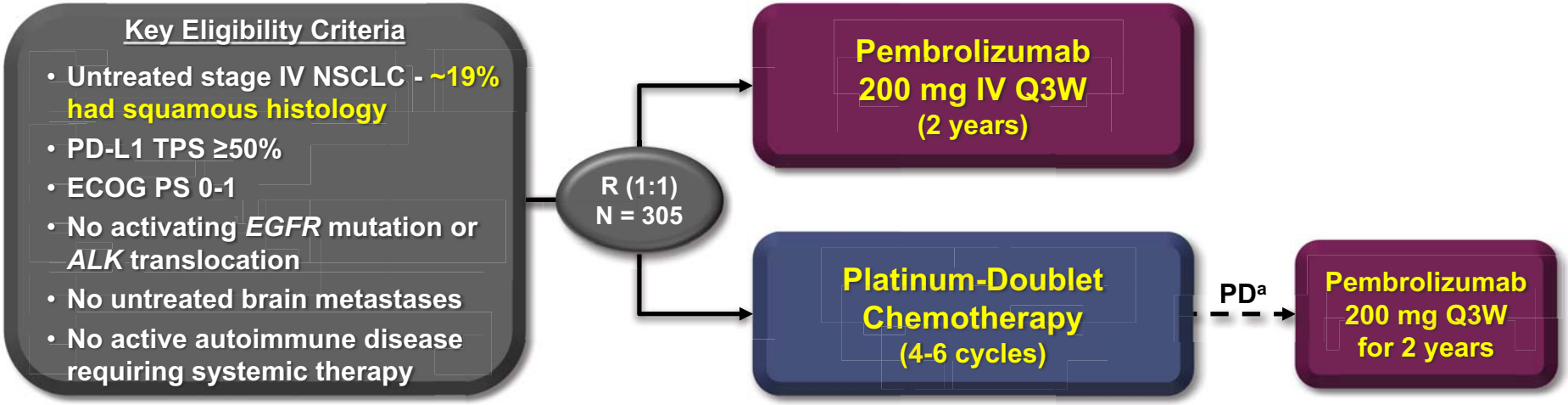
S0819 (SqCLC-EGFR FISH+)[2]



FISH, fluorescent in situ hybridization; GC, gemcitabine and cisplatin; N, necitumumab

1. Hirsch et al., WCLC 2015;abstr ORAL32.05; 2. Herbst et al., WCLC 2015;abstr PLEN04.01;

KEYNOTE-024 Study Design (NCT02142738)



Key End Points

Primary: PFS (RECIST v1.1 per blinded, independent central review)

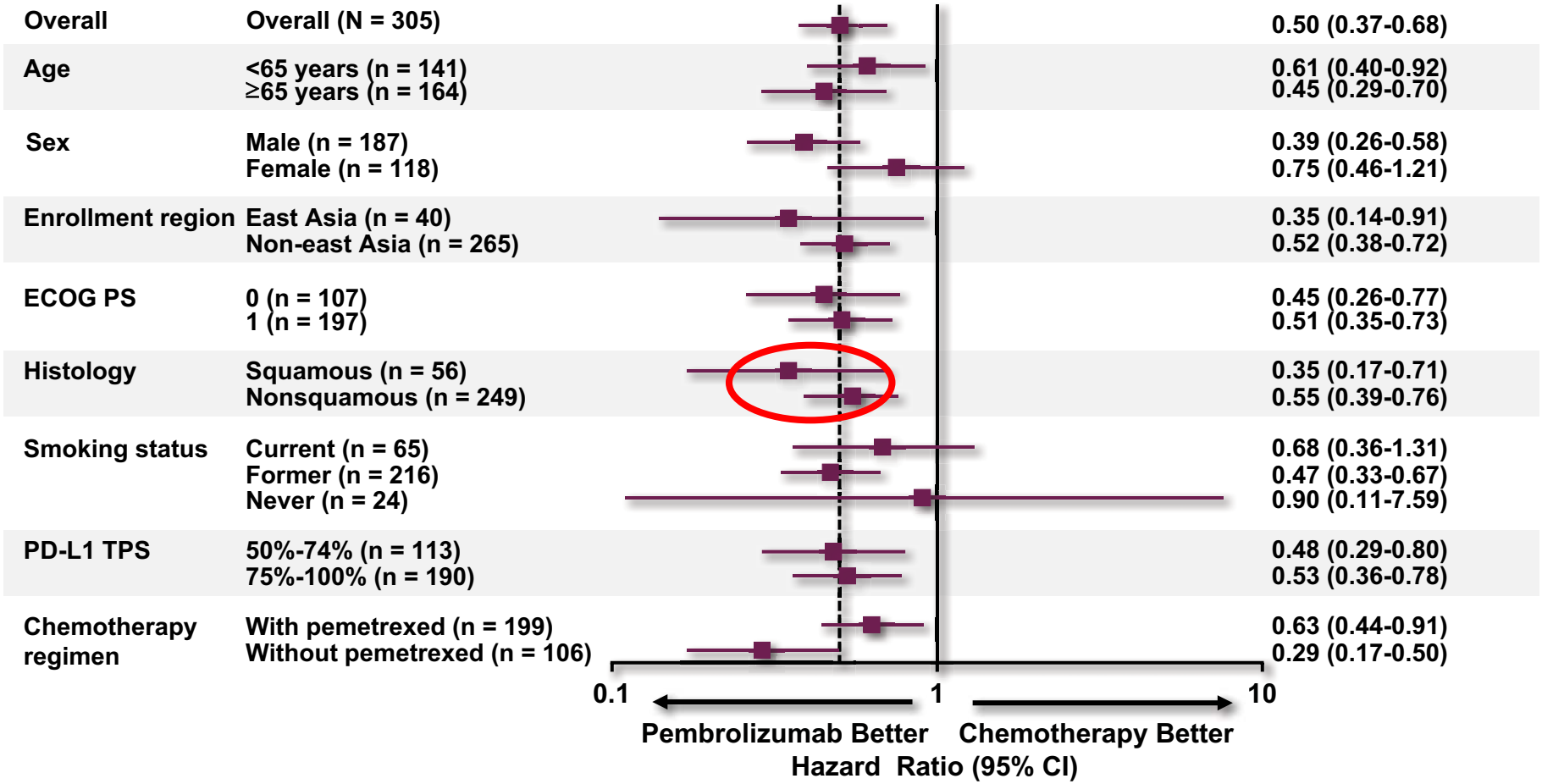
Secondary: OS, ORR, safety

Exploratory: DOR

Reck M et al. *N Engl J Med* 375:1823-33, 2016

[a]To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.

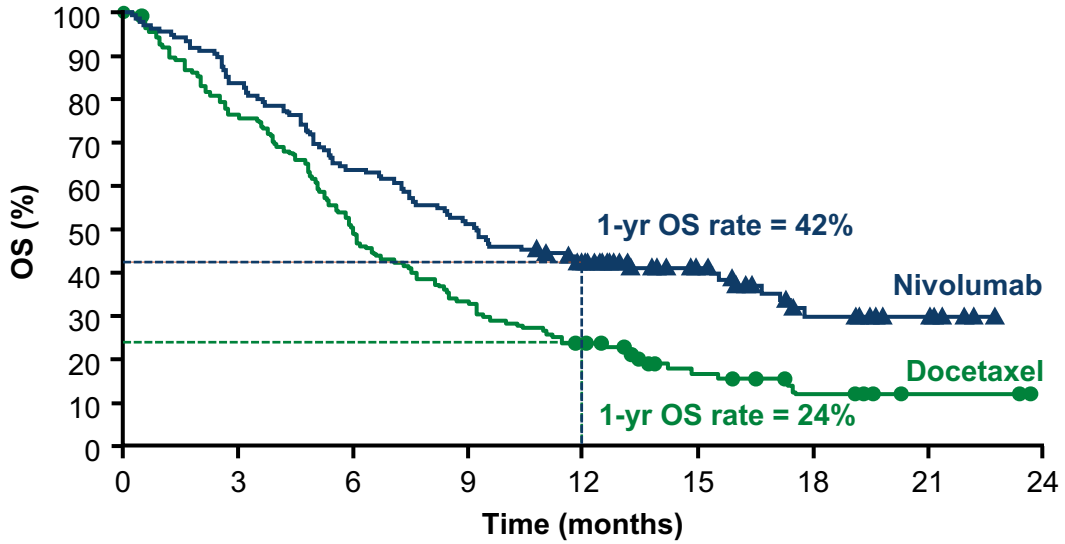
Progression-Free Survival in Subgroups



Vertical dotted line represents HR in the total population.

Data cut-off: May 9, 2016.

CheckMate-017: Nivolumab Vs Docetaxel – 2nd Line Squamous Carcinoma: Overall Survival



Number of Patients at Risk

Nivolumab	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

Symbols represent censored observations

	Nivolumab n = 135	Docetaxel n = 137
mOS mo, (95% CI)	**9.2** (7.3, 13.3)	**6.0** (5.1, 7.3)
mPFS, mo (95% CI)	**3.5** (2.1, 4.9)	**2.8** (2.1, 3.5)

OS HR = 0.59 (95% CI: 0.44, 0.79), ***p* = 0.00025**

PFS HR = 0.62 (95% CI: 0.47, 0.81) ***p* = 0.0004**

ORR – 20% versus 9%, *p* = 0.0083

Brahmer J et al. *N Engl J Med* 373:123-35, 2015.

REVEL: Docetaxel ± Ramucirumab in the 2nd Line Setting*

ORR – 22.9 vs 13.6%, $p<0.001$

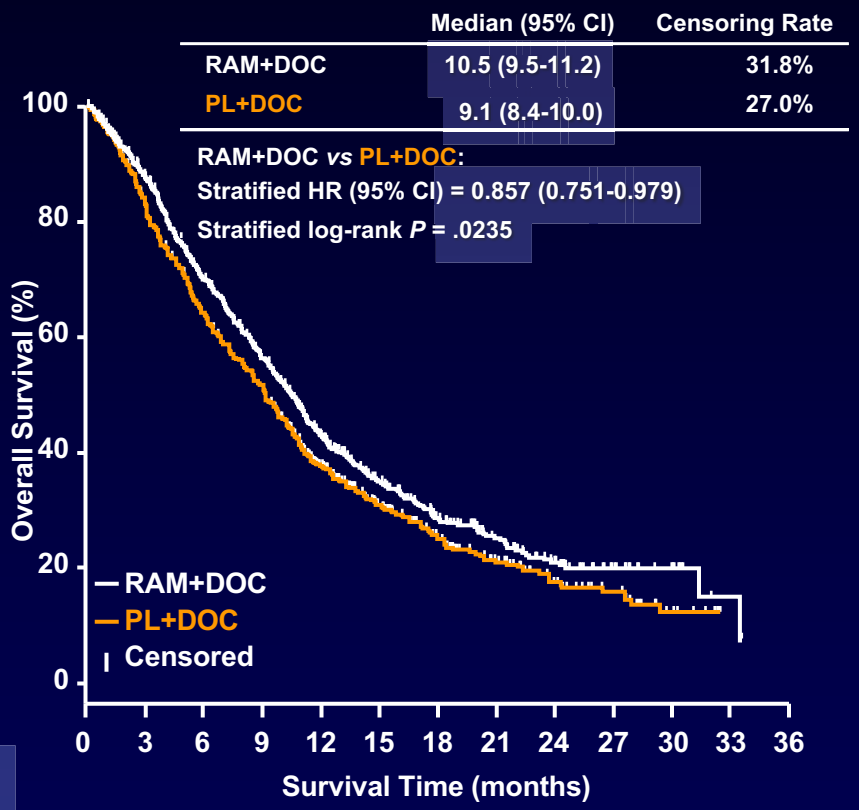
DCR – 64.0 vs 52.6%, $p<0.001$

PFS – HR = 0.76, $p<0.0001$

Toxicities (Gr 3-4) – F/N 15.9 vs 10.0%, stomatitis 4.9 vs 1.6%

No ↑ in gr 3-4 hemorrhage but gr 1-2 hemorrhage was 26.5 vs 12.9% (largely epistaxis)

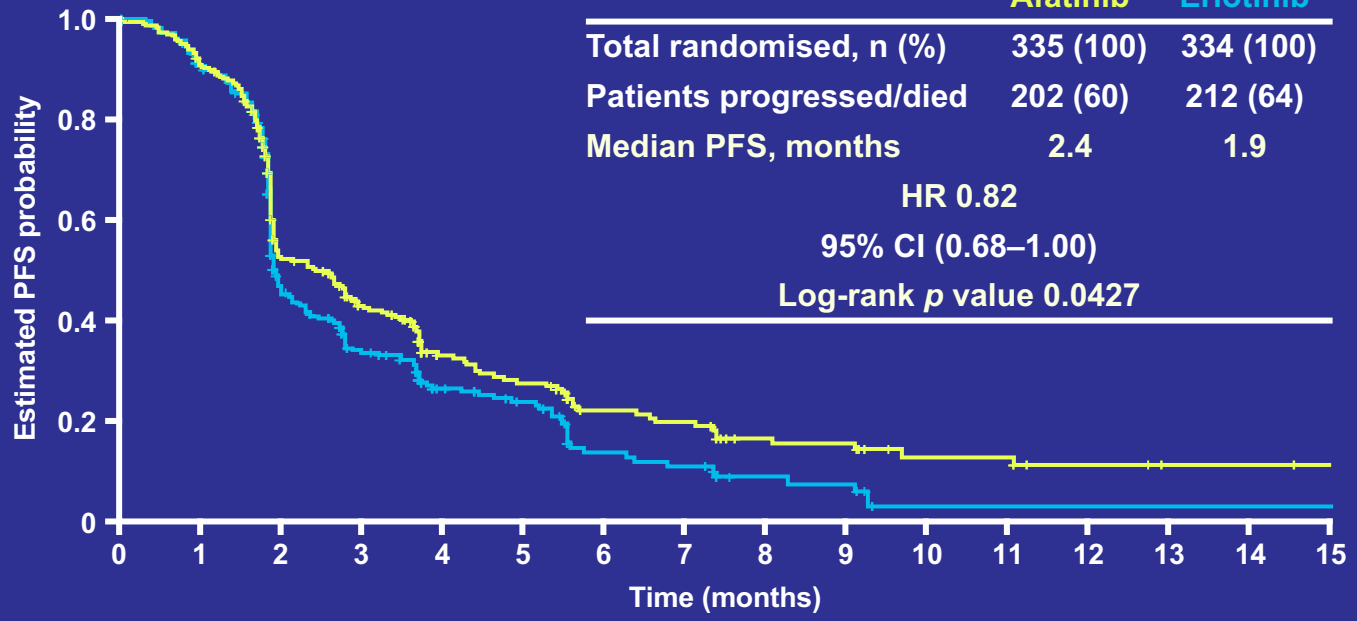
OS HR for squamous subset was 0.88 (p=NS)



*328 of 1240 (26%) patients had squamous histology

Garon EB et al. *Lancet* 93:95-103, 2014

LUX-Lung 8: Afatinib Vs Erlotinib in 2nd Line Squamous Carcinoma: PFS, independent review (1^0 Endpoint)



	Afatinib	Erlotinib
Total randomised, n (%)	335 (100)	334 (100)
Patients progressed/died	202 (60)	212 (64)
Median PFS, months	2.4	1.9

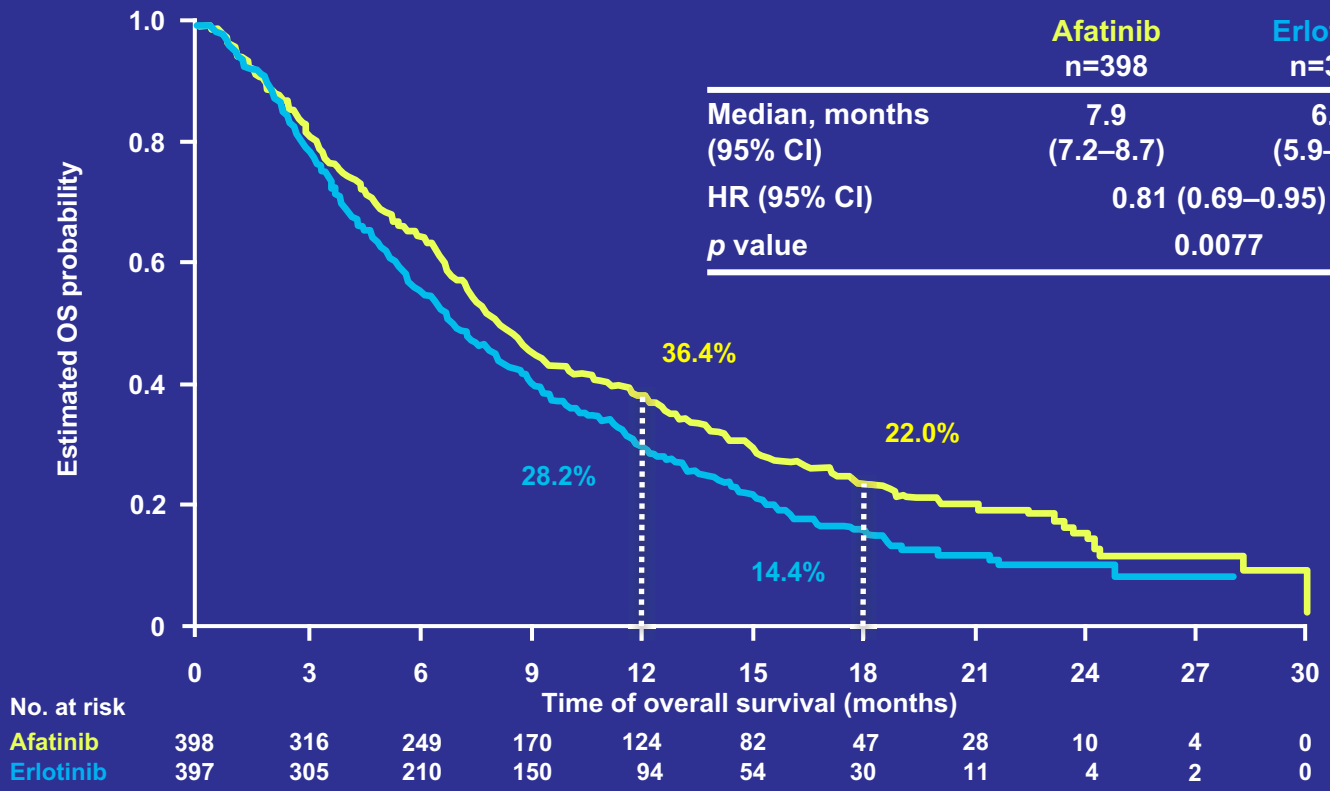
HR 0.82

95% CI (0.68–1.00)

Log-rank *p* value 0.0427

CI, confidence interval; HR, hazard ratio

Primary analysis of OS (n=795)



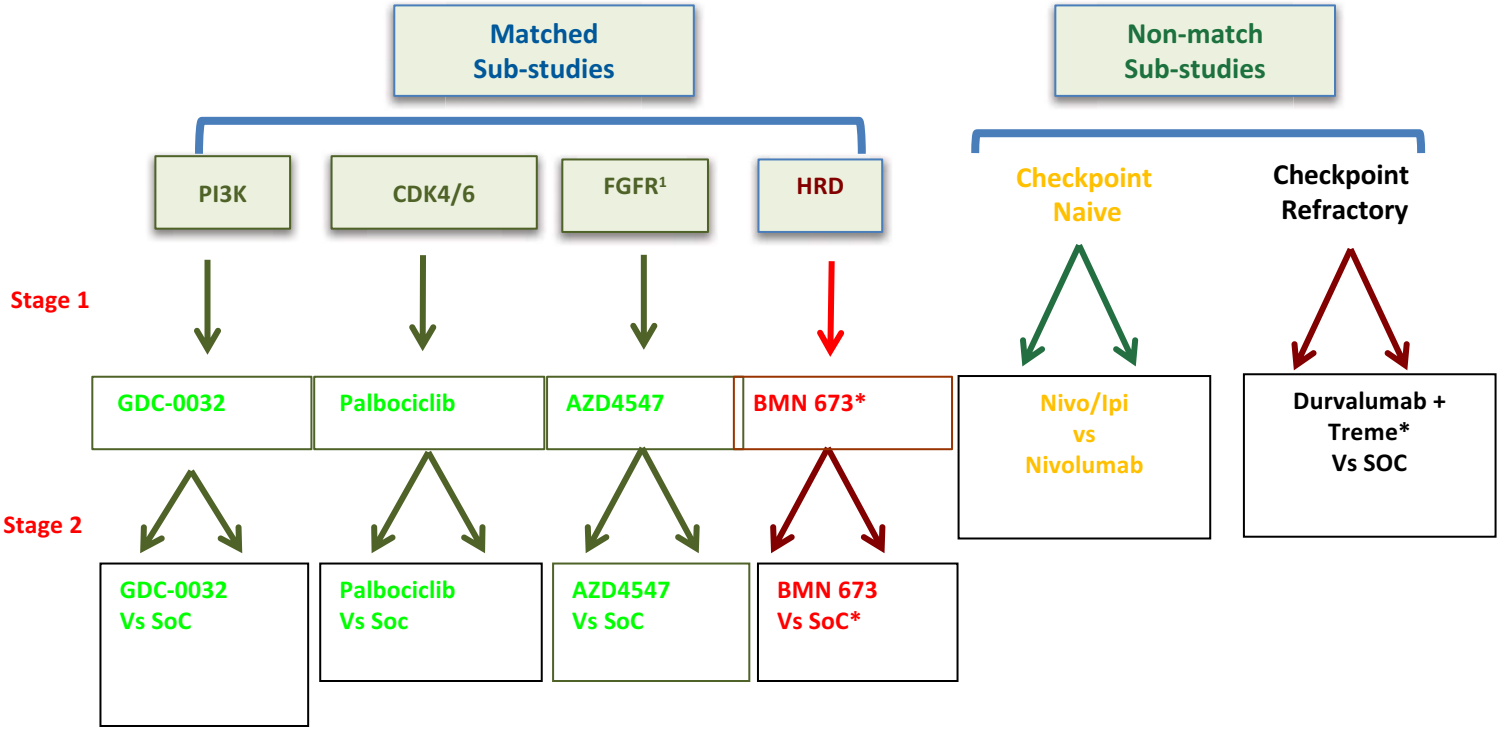
	Afatinib n=398	Erlotinib n=397
Median, months (95% CI)	7.9 (7.2–8.7)	6.8 (5.9–7.8)
HR (95% CI)	0.81 (0.69–0.95)	
p value	0.0077	

Median follow-up time: 18.4 months

Recent Phase III Trials - 2nd Line Squamous Carcinoma

Trial	Comparison	HR for OS	HR for PFS	ORR (%)
CheckMate-017	Nivolumab vs Docetaxel	**0.59** ***p*=0.00025**	**0.62** ***p*=0.0004**	**20 vs 9** ***p*=0.0083**
REVEL	Docetaxel ± Ramucirumab	**0.85** ***p*=0.023**	**0.76** ***p*<0.0001**	**22.9 vs 13.6** ***P*<0.001**
REVEL - Squamous	"	**0.88** ***p*=ns**	**0.76** ***p*=0.019**	**NS**
LUX-Lung 8	Afatinib Vs Erlotinib	**0.81** ***p*=0.0077**	**0.82** ***p*=0.04**	**6 vs 3**

2nd Line Squamous NSCLC - Updated Lung-MAP Trial Schema (2016 with Revs # 3 & 4)



- **Lung-MAP amended to 2nd line therapy & beyond to accommodate Nivolumab approval**
- **Pre-screening added back**
- **Eligibility criteria broadened; *Sub-studies in development**

CDK, cyclin D-dependent kinase; FGFR, fibroblast growth factor receptor; HRD, Homologous Recombination Defects; Ipi, ipilimumab; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; SoC, standard-of-care

1. Lung-MAP. Available at: http://www.lung-map.org/healthcare-providers. Accessed February, 2016

Key Take Home Points – Stage IV Squamous

- PD-L1 testing should be done on all newly diagnosed stage IV squamous carcinoma patients
- If > 50% PD-L1+, pembrolizumab is the optimal treatment
- Platinum-based doublets remain the SoC in 1st line treatment of stage IV squamous carcinoma of the lung – I prefer taxanes……
- Immunotherapy is the SoC for the majority of patients in the 2nd line setting (nivolumab, pembrolizumab & atezolizumab)
- 3rd line options – docetaxel ± ramucirumab, afatinib
- Genomic analyses have identified several potential targets none of which have been validated to date